NHS England Evidence Review:

Vemurafenib plus rituximab for relapsed or refractory classic hairy cell leukaemia

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Vemurafenib plus rituximab for relapsed or refractory classic hairy cell leukaemia

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of *v*emurafenib plus rituximab compared to current standard care for relapsed or refractory classic hairy cell leukaemia (HCL).

HCL is a very rare type of leukaemia (blood cancer) which is characterised by a mutation called BRAF V600 which is present in all leukaemic cells. Classic HCL predominantly affects middle-aged individuals and is more common in males than females. Symptoms of classic HCL can include weight loss, weakness and frequent infections, but approximately 25% of patients have no symptoms at the time of diagnosis and are identified based on the findings of routine blood tests. The majority of patients with classic HCL will require treatment soon after diagnosis.

The first line treatment for patients with classic HCL is purine nucleoside analogue (PA) therapy and current standard care is single agent PA therapy (with either cladribine or pentostatin). For patients who are refractory to, or relapse within 2 years following PA therapy, standard second line treatment is generally with an alternative PA therapy in combination with rituximab. Patients who are refractory to, or relapse within 2 to 5 years following PA therapy can be retreated with the initial PA therapy plus rituximab. Patients who relapse beyond 5 years from the end of initial treatment with PA therapy can be re-treated with the same, or an alternative, single agent PA therapy, plus or minus rituximab.

The combination of vemurafenib plus rituximab is proposed as a possible treatment for patients who are refractory to, or later relapse following, treatment with a second line PA therapy plus or minus rituximab, or who are unsuitable for PA therapy either first or second line.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from vemurafenib plus rituximab more than others and the treatment duration and dose of vemurafenib plus rituximab that was used.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of vemurafenib plus rituximab compared to current standard care for patients with classic hairy cell leukaemia (HCL) who are refractory to, or later relapse following, treatment with second line purine analogue (PA) therapy +/- rituximab, or patients with classic HCL who are unsuitable for PA therapy either first or second line.

The searches for evidence published since January 2013 were conducted on 31st August 2023 and identified 111 references. The titles and abstracts were screened and 12 full text papers were obtained and assessed for relevance.

Two papers were identified for inclusion. One was a prospective case series (Tiacci et al 2021) which reported progression free survival, relapse free survival, response to treatment and adverse event outcomes in up to 31 patients in Italy, at timepoints ranging from four weeks to 37 months after the completion of treatment. The second was a retrospective case series (Robak et al 2021) which reported relapse free survival, response to treatment and adverse event outcomes in three patients in Poland at up to 38 months after completion of treatment. No comparative studies were identified and there were no studies reporting cost effectiveness.

In terms of clinical effectiveness:

- **Progression free survival (critical outcome)**
    - One prospective case series provided very low certainty evidence of 78% progression[1] free survival at median 37 months follow-up. It also provided very low certainty evidence of 85% relapse[2] free survival at median 34 months follow-up, while a retrospective case series provided very low certainty evidence of relapse[3] free survival in three out of patients at 13 months, two of three at 18 months and one of three at 38+ months. The prospective case series also provided very low certainty evidence that 100% of patients who were minimal residual disease (MRD[4])-negative after the end of treatment remained MRD-negative at median 28.5 months follow-up.
- **Response to treatment (critical outcome)**
    - One prospective case series provided very low certainty evidence of complete response[5] in 86.7% patients (65% of whom had no MRD) and partial response[6] in 3.3%. One retrospective case series provided very low certainty evidence of complete response in two out of three patients and haematological response[7] in one of three.

[1] Progression was defined as HCL-related death, relapse, or worsening of cytopaenias, whichever occurred first, after the start of treatment.
[2] Relapse was defined in this study as the reappearance of HCL-related cytopaenia in patients who had previously had a response at the end of treatment.
[3] Relapse was not consistently defined in this study.
[4] MRD was assessed in bone marrow aspirates and in peripheral blood by means of allele-specific DNA PCR testing for BRAF V600E (sensitivity, ≥0.05% mutant copies).
[5] Complete response was defined as the resolution of cytopaenias (Hb≥11g/dl, neutrophil count ≥1500/mm^3, or platelet count ≥100,000/mm^3), no palpable splenomegaly, and no hairy cells morphologically visible in the bone marrow biopsy and blood-smear samples
[6] Partial response was defined as the resolution of cytopaenias and a reduction of at least 50% in splenomegaly and in HCL infiltration in the bone marrow biopsy sample on immunohistochemical testing
[7] Complete response was not defined in this study; haematological response was defined as the resolution of cytopaenia.

- **Overall survival (critical outcome)**
    - no evidence was identified.
- **Unplanned hospital admissions due to treatment-related adverse events (important outcome)**
    - no evidence was identified.
- **Incidence of treatment-related infection (important outcome)**
    - One prospective case series provided very low certainty evidence that no patients had a treatment-related infection.
- **Quality of life (important outcome)**
    - no evidence was identified.
- **Activities of daily living (important outcome)**
    - no evidence was identified.

In terms of safety:

- **Adverse effects**
    - One prospective case series provided very low certainty evidence that while adverse events associated with treatment appeared quite common, most were grade 1-2 and transient. One retrospective case series provided very low certainty evidence that none out of three patients had a serious adverse event.

In terms of subgroups:

- One prospective case series carried out a number of unplanned subgroup analyses, reporting relapse free survival among patients who had had a complete response to treatment according to a number of criteria. At a median follow-up of 34 months relapse free survival was 57% among patients who had previously been treated with a BRAF inhibitor and 95% among patients who had not previously been treated with a BRAF inhibitor. At an unspecified duration of follow-up relapse free survival was 100% among patients who had no MRD and 56% among patients who had MRD. At an unspecified duration of follow-up relapse free survival was 89% among patients who had received rituximab previously and 82% among patients who had not received rituximab previously.

Dose of vemurafenib and rituximab used:

- In the prospective case series patients received oral vemurafenib (960 mg twice daily) for a total of eight weeks, and eight intravenous rituximab infusions (375 mg/m^2) administered over a period of 18 weeks. Almost half (14/29) patients received a reduced dose of vemurafenib (720mg or 480mg twice daily) for at least two weeks during treatment due to toxic effects, but in 10/14 the dose was re-escalated once the toxic effects resolved.
- In the retrospective case series patients received a lower dose but longer duration of vemurafenib (240 mg twice daily for 16 weeks) and had eight infusions of the same dose of rituximab (375mg/m^2) every two weeks over 16 weeks.

Please see the results table (section 5) in the review for further details of outcomes.

Limitations

Both studies had a high risk of bias and certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE. Limitations reducing certainty in the outcomes reported include the lack of comparator groups, the small numbers of subjects and uncertainty about whether inclusion was complete and consecutive, the retrospective design and limited detail in Robak et al 2021, and the lack of statistical analysis. While the prospective case series provided definitions of response and relapse, these were not clearly defined in the retrospective case series[8]. The two studies used different treatment regimes for vemurafenib plus rituximab.

Conclusion

The studies identified for this review provide very low certainty evidence for the critical and important outcomes of progression free survival, relapse free survival, survival free of MRD, and response to treatment, and for the important outcomes of incidence of treatment-related infection and safety. No evidence was identified for the critical outcome of overall survival or the important outcomes of unplanned hospital admissions related to treatment-related adverse events, quality of life and activities of daily living, and no evidence on cost effectiveness was found. No comparative studies were identified.

The prospective case series reported that at median 37 months follow-up from the start of treatment progression free survival was 78%, and at median 34 months follow-up from treatment completion relapse free survival among patients who had had a complete response to treatment was 85%. It also reported that all patients who were MRD-negative after the end of treatment remained free of MRD at median 28.5 months follow-up.

The evidence from the prospective case series also found that 86.7% of patients had a complete response to treatment and 3.3% had a partial response (the remaining patients being unevaluable). In a retrospective case series with only three subjects two had a complete response and one had a haematological response. Adverse events associated with treatment were common but most were low grade and all were reported to be transient. No patients were reported to have treatment-related infections.

Unplanned subgroup analyses reported a higher rate of relapse free survival among patients who had not previously been treated with a BRAF inhibitor compared with those who had previously been treated with a BRAF inhibitor, and among patients who had no MRD at treatment completion compared with those who had MRD. Relapse free survival was similar among those who had and had not received rituximab previously. However no statistical tests were reported for these comparisons so it is not possible to comment on the significance of these findings.

The very low certainty evidence identified suggests that the majority of patients with relapsed or refractory classic hairy cell leukaemia respond to treatment with vemurafenib plus rituximab, with few serious or sustained adverse effects. The limitations of the studies

[8] Tiacci et al 2021 defined complete response as the resolution of cytopaenias (Hb≥11g/dl, neutrophil count ≥1500/mm^3, or platelet count ≥100,000/mm^3), no palpable splenomegaly, and no hairy cells morphologically visible in the bone marrow biopsy and blood-smear samples, and partial response as the resolution of cytopaenias and a reduction of at least 50% in splenomegaly and in HCL infiltration in the bone marrow biopsy sample on immunohistochemical testing. Relapse was defined as the reappearance of HCL-related cytopaenia in patients who had previously had a response at the end of treatment. Robak et al 2021 defined haematological response as the resolution of cytopaenia but did not provide consistent definitions of complete response or relapse.

limit the strength of the conclusions that can be drawn and the lack of comparative data mean that no conclusions can be drawn about the effectiveness of vemurafenib plus rituximab compared with other treatments.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In people with classic HCL who are refractory to, or later relapse following, treatment with second line PA therapy +/- rituximab OR patients with classic HCL who are unsuitable for PA therapy either first or second line, what is the clinical effectiveness of vemurafenib plus rituximab plus standard care compared with standard care alone OR standard care with rituximab, interferon alpha-2a therapy, splenectomy or palliative care?
2. In people with classic HCL who are refractory to, or later relapse following, treatment with second line PA therapy +/- rituximab OR patients with classic HCL who are unsuitable for PA therapy either first or second line, what is the safety of vemurafenib plus rituximab plus standard care compared with standard care alone OR standard care with rituximab, interferon alpha-2a therapy, splenectomy or palliative care?
3. In people with classic HCL who are refractory to, or later relapse following, treatment with second line PA therapy +/- rituximab OR patients with classic HCL who are unsuitable for PA therapy either first or second line, what is the cost effectiveness of vemurafenib plus rituximab plus standard care compared with standard care alone OR standard care with rituximab, interferon alfa-2a therapy, splenectomy or palliative care?
4. From the evidence selected, are there any subgroups of patients that may benefit from vemurafenib plus rituximab more than the wider population of interest?
5. From the evidence selected, what was the treatment duration and dosing of vemurafenib plus rituximab in the population of interest?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 31st August 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Two studies were identified for inclusion. One was a prospective case series which reported survival, response to treatment and adverse event outcomes in up to 31 patients, at from four weeks to 37 months after the completion of treatment. The second was a retrospective case series which reported response to treatment and adverse event outcomes in three patients at up to 38 months after completion of treatment. No comparative studies were identified and there were no studies reporting cost effectiveness.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Robak et al 2021 Retrospective case record review Lodz, Poland	Patients with classic HCL who had relapsed following treatment with Moxetumomab. All had previously been treated with cladribine. All were positive for BRAF p.V600E. Total sample size: n=3 Age range 28-53 years Male 2, Female 1	**Intervention** Vemurafenib 240 mg twice daily for 16 weeks + rituximab 375mg/m^2 intravenously every 2 weeks x 8. **Comparison** No comparator group	**Critical outcomes** • Relapse free survival • Response to treatment **Important outcomes** • Safety ○ Serious adverse events associated with treatment
Tiacci et al 2021 Prospective case series Perugia, Italy	Patients with HCL and mutated BRAF V600E who were refractory to, or had relapsed after, or were unsuitable for purine analogue (PA) therapy. All patients had cytopaenia (Hb<11g/dl, neutrophil count <1500/mm^3, or platelet count <100,000/mm^3). Total sample size: n=31 Median age 61 years (range, 35 to 81) Male 28, Female 3	**Intervention** Oral vemurafenib (960 mg twice daily for 8 weeks, and 8 intravenous rituximab infusions (375 mg/m^2 of body-surface area) administered over a period of 18 weeks **Comparison** No comparator group	**Critical outcomes** • Progression free survival • Relapse free survival • Survival free from minimal residual disease • Response to treatment **Important outcomes** • Incidence of treatment-related infection • Safety ○ Adverse events associated with treatment

5. Results

In people with classic HCL who are refractory to, or later relapse following, treatment with second line PA therapy +/- rituximab OR patients with classic HCL who are unsuitable for PA therapy either first or second line, what is the clinical effectiveness and safety of vemurafenib plus rituximab plus standard care compared with standard care alone OR standard care with rituximab, interferon alpha-2a therapy, splenectomy or palliative care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Overall survival **Certainty of evidence:** Not applicable	Overall survival is important to patients as individuals with relapsed or refractory HCL have a high mortality rate due to advanced disease. Improved overall survival is an important marker of effective treatment. **No evidence was identified for overall survival**
Progression free survival **Certainty of evidence:** Very low	Progression free survival is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures. One prospective case series provided evidence relating to progression free survival and survival free of minimal residual disease (MRD), and one prospective and one retrospective case series provided evidence relating to relapse free survival in patients with classic HCL who are refractory to or relapse following treatment with second line PA therapy +/- rituximab, or who are unsuitable for PA therapy first or second line. *Progression free survival* **At median 37 months (range 0.5 to 54.5) follow-up from the start of treatment:** • One prospective case series (Tiacci et al 2021) (n=30) reported progression[9] free survival of 78%. **(VERY LOW)** *Relapse free survival* **At between 13 and 38+ months after the end of treatment:** • One retrospective case series (Robak et al 2021) (n=3) reported relapse[10] free survival in 3/3 patients at 13 months, 2/3 at 18 months and 1/3 at 38+ months. **(VERY LOW)** **At median 34 months (range 13 to 50) follow-up from the end of treatment:** • One prospective case series (Tiacci et al 2021) (n=26 patients who had had a complete response to treatment) reported relapse[11] free survival of 85% (22/26). **(VERY LOW)**

[9] Progression was defined as HCL-related death, relapse, or worsening of cytopaenias, whichever occurred first, after the start of treatment.
[10] Relapse was not consistently defined in this study.

Outcome	Evidence statement
	Survival free of MRD **At median 28.5 months (range 21 to 50) follow-up from when MRD status was first observed:** • One prospective case series (Tiacci et al 2021) (n=17 patients who were MRD-negative after the end of treatment) reported survival free of MRD in both bone marrow and peripheral blood of 100%. **(VERY LOW)** **One prospective case series provided very low certainty evidence of 78% progression free survival at a median 37 months follow-up. It also provided very low certainty evidence of 85% relapse free survival at median 34 months follow-up, while a retrospective case series provided very low certainty evidence of relapse free survival in three out of three patients at 13 months, two of three at 18 months and one of three at 38+ months. The prospective case series also provided very low certainty evidence that 100% of patients who were MRD-negative after the end of treatment remained MRD-negative at median 28.5 months follow-up.**
Response to treatment **Certainty of evidence:** Very low	Response to treatment is important to patients as it represents whether the treatment can improve disease burden. One prospective and one retrospective case series provided evidence relating to response to treatment in patients with classic HCL who are refractory to or relapse following treatment with second line PA therapy +/- rituximab, or who are unsuitable for PA therapy first or second line. **After treatment completion:** • One retrospective case series (Robak et al 2021) (n=3) reported complete response[12] in 2/3 patients and haematological response in 1/3. **(VERY LOW)** **At 4 weeks after treatment completion:** • One prospective case series (Tiacci et al 2021) (n=30) reported complete response[13] in 86.7% (26/30) patients (p=0.005). **(VERY LOW)** • One prospective case series (Tiacci et al 2021) (n=30) reported partial response[14] in 3.3% (1/30) patients. **(VERY LOW)** • One prospective case series (Tiacci et al 2021) (n=30) reported that 3/30 patients were not evaluable[15]. **(VERY LOW)** • One prospective case series (Tiacci et al 2021) (n=26 patients who had had a complete response to treatment) reported that 65% (17/26) patients had no minimal residual disease[16]. **(VERY LOW)**

[11] Relapse was defined in this study as the reappearance of HCL-related cytopaenia in patients who had previously had a response at the end of treatment.
[12] Complete response was not defined; haematological response was defined as the resolution of cytopaenia.
[13] Complete response was defined as the resolution of cytopaenias (Hb≥11g/dl, neutrophil count ≥1500/mm^3, or platelet count ≥100,000/mm^3), no palpable splenomegaly, and no hairy cells morphologically visible in the BM biopsy and blood-smear samples
[14] Partial response was defined as the resolution of cytopaenias and a reduction of at least 50% in splenomegaly and in HCL infiltration in the BM biopsy sample on immunohistochemical testing
[15] One died after 10 days' treatment due to pre-existing infection; two did not receive full courses of treatment due to persistent toxic effects or concomitant myelodysplasia
[16] MRD was assessed in BM aspirates and in peripheral blood by means of allele-specific DNA PCR testing for BRAF V600E (sensitivity, ≥0.05% mutant copies).

Outcome	Evidence statement
	One prospective case series provided very low certainty evidence of complete response in 86.7% patients (65% of whom had no MRD) and partial response in 3.3%. One retrospective case series provided very low certainty evidence of complete response in two out of three patients and haematological response in one of three.
Important outcomes	
Unplanned hospital admissions due to treatment-related adverse events **Certainty of evidence:** Not applicable	This is an important outcome to patients and their carers because it reflects the tolerability and adverse effects of the treatment. From a service delivery perspective, it reflects the demands placed on the healthcare system for the intervention. **No evidence was identified for unplanned hospital admissions due to treatment-related adverse events**
Incidence of treatment-related infection **Certainty of evidence:** Very low	This is an important outcome to patients and their carers because it is an important potential complication of treatment. One prospective case series provided evidence relating to treatment-related infection. **At an unspecified duration of follow-up:** • One prospective case series (Tiacci et al 2021) (n=31) reported that no patients had a treatment-related infection. **(VERY LOW)** **One prospective case series provided very low certainty evidence that no patients had a treatment-related infection.**
Quality of life **Certainty of evidence:** Not applicable	Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making and inform health policy. **No evidence was identified for quality of life**
Activities of daily living (ADLs) **Certainty of evidence:** Not applicable	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. **No evidence was identified for activities of daily living**
Safety	
Safety outcomes **Certainty of evidence:** Very low	The safety of vemurafenib and rituximab is important to patients as it informs treatment decisions and allows comparison of interventional approaches. One prospective and one retrospective case series provided evidence relating to adverse events in patients with classic HCL who are refractory to or relapse following treatment with second line PA therapy +/- rituximab, or who are unsuitable for PA therapy first or second line. • One prospective case series (Tiacci et al 2021) (n=31) reported that 9 (29%) patients had an infusion-related reaction associated with rituximab. They also reported adverse events (most grade 1-2 and reported to be transient) associated with vemurafenib including asymptomatic hyperbilirubinemia in 24 (77%), asymptomatic increase in pancreatic enzymes in 18 (58%), arthralgia or arthritis in 17 (55%), rash or erythema in 15 (48%), skin papilloma or warts in 14 (45%), asymptomatic increase in aspartate or alanine aminotransferase level in 9 (29%), asymptomatic increase in γ-glutamyltransferase or alkaline phosphatase level in 9 (29%), asymptomatic hypophosphatemia in 9 (29%) and anaemia in 7

Outcome	Evidence statement
	(23%). A large number of less common adverse events were also reported. In 14/29 patients there were toxic effects requiring reduction of the dose of vemurafenib for at least 2 weeks. **(VERY LOW)** • One retrospective case series (Robak et al 2021) (n=3) reported that 0/3 patients had serious adverse effects associated with treatment. **(VERY LOW)** **One prospective case series provided very low certainty evidence that while adverse events associated with treatment appeared quite common, most were grade 1-2 and transient. One retrospective case series provided very low certainty evidence that none out of three patients had a serious adverse event.**
Abbreviations BM: bone marrow; HCL: hairy cell leukaemia; MRD: minimal residual disease; PA: purine analogue	

In people with classic HCL who are refractory to, or later relapse following, treatment with second line PA therapy +/- rituximab OR patients with classic HCL who are unsuitable for PA therapy either first or second line, what is the cost effectiveness of vemurafenib plus rituximab plus standard care compared with standard care alone OR standard care with rituximab, interferon alpha-2a therapy, splenectomy or palliative care?

Outcome	Evidence statement
Cost effectiveness	No evidence was identified for cost effectiveness

From the evidence selected, are there any subgroups of patients that may benefit from vemurafenib plus rituximab more than the wider population of interest?

Subgroup	Evidence statement
Previous treatment with a BRAF inhibitor	**At median 34 months follow-up:** • One prospective case series (Tiacci et al 2021) (n=26 who had a complete response to treatment) reported relapse free survival of 57% in n=7 patients previously treated with a BRAF inhibitor, and 95% in n=19 patients not previously treated with a BRAF inhibitor
Presence or absence of MRD	**At unspecified duration of follow-up:** • One prospective case series (Tiacci et al 2021) (n=26 who had a complete response to treatment) reported relapse free survival of 100% in n=17 patients who had no MRD, and 56% in n=9 patients who had MRD.
Previous exposure to rituximab	**At unspecified duration of follow-up:** • One prospective case series (Tiacci et al 2021) (n=26 who had a complete response to treatment) reported relapse free survival of 89% in n=9 patients who had received rituximab previously, and 82% in n=17 patients who had not received rituximab previously.
Abbreviations MRD: minimal residual disease	

From the evidence selected, what was the treatment duration and dosing of vemurafenib plus rituximab in the population of interest?

Outcome	Evidence statement
Dose of vemurafenib plus rituximab	In Tiacci et al 2021 (prospective case series) patients received oral vemurafenib (960 mg twice daily) for 8 weeks, and 8 intravenous rituximab infusions (375 mg/m^2 of body-surface area) administered over a period of 18 weeks. Treatment was administered in two cycles each consisting of 4 weeks of vemurafenib with rituximab infusions on days 1 and 15, followed by 2 weeks of rest and response evaluation. After the second cycle, four additional doses of rituximab were administered 2 weeks apart from one another. 14/29 patients received a reduced dose of vemurafenib (720mg or 480mg twice daily for at least 2 weeks) due to toxic effects. In 10/14 the dose was re-escalated once the toxic effects resolved. In Robak et al 2021 (retrospective case series) patients received vemurafenib 240 mg twice daily for 16 weeks + rituximab 375mg/m^2 intravenously every 2 weeks x 8.

6. Discussion

This evidence review examines the clinical effectiveness, safety and cost effectiveness of vemurafenib plus rituximab in people with classic hairy cell leukaemia (HCL) who are refractory to, or later relapse following, treatment with second line purine analogue (PA) therapy +/- rituximab, or patients with classic HCL who are unsuitable for PA therapy either first or second line. The critical outcomes of interest were overall survival, progression free survival and response to treatment. Important outcomes were unplanned hospital admissions related to treatment-related adverse events, incidence of treatment-related infection, quality of life, activities of daily living and safety. Evidence was also sought on cost effectiveness.

Evidence was available from one prospective case series (Tiacci et al 2021) which reported progression free and relapse free survival, response to treatment and adverse event outcomes in up to 31 patients, at from four weeks to 37 months after the completion of treatment, and one retrospective case series (Robak et al 2021) which reported relapse free survival, response to treatment and adverse event outcomes in three patients at up to 38 months after completion of treatment. No comparative studies were identified and there were no studies reporting cost effectiveness.

Both papers defined inclusion criteria although neither stated whether inclusion of patients was consecutive or complete. All patients in both studies were reported to have the BRAF V600E mutation but one patient recruited to Tiacci et al 2021 was withdrawn after commencing the study as they were found to have an unclassifiable B-cell neoplasm instead of HCL.

Tiacci et al 2021 clearly defined their outcomes and described how assessments were carried out while this detail was not provided for all patients included in Robak et al 2021[17]. The length of follow-up was clearly stated in both studies for all critical and important outcomes. The analyses reported in Tiacci et al 2021 were intention-to-treat. They also provided details of adverse events graded 1-4 according to the Common Terminology Criteria for Adverse Events, while Robak et al 2021 only stated that there were no serious adverse events.

Tiacci et al 2021 also reported subgroup analyses, which had not been pre-specified but were described 'hypothesis-generating', which compared relapse free survival in those who had had a complete response to treatment depending on whether they had previously had treatment with a BRAF inhibitor, whether or not they had minimal residual disease (MRD) at treatment completion, and whether or not they had previously received rituximab.

The dose of vemurafenib plus rituximab differed between the two studies. In Tiacci et al 2021 patients received oral vemurafenib (960 mg twice daily) for a total of eight weeks, and eight intravenous rituximab infusions (375 mg/m^2) administered over a period of 18 weeks. Almost half (14/29) patients received a reduced dose of vemurafenib (720mg or 480mg twice daily) for at least two weeks during treatment due to toxic effects, but in 10/14 the

[17] Tiacci et al 2021 defined complete response as the resolution of cytopaenias (Hb≥11g/dl, neutrophil count ≥1500/mm^3, or platelet count ≥100,000/mm^3), no palpable splenomegaly, and no hairy cells morphologically visible in the bone marrow biopsy and blood-smear samples, and partial response as the resolution of cytopaenias and a reduction of at least 50% in splenomegaly and in HCL infiltration in the bone marrow biopsy sample on immunohistochemical testing. Relapse was defined as the reappearance of HCL-related cytopaenia in patients who had previously had a response at the end of treatment. Robak et al 2021 defined haematological response as the resolution of cytopaenia but did not provide consistent definitions of complete response or relapse.

dose was re-escalated once the toxic effects resolved. In Robak et al 2021 patients received a lower dose but longer duration of vemurafenib (240 mg twice daily for 16 weeks) and had eight infusions of the same dose of rituximab (375mg/m^2) every two weeks over 16 weeks.

Only one p value was reported (in Tiacci et al 2021) but it was not described how this had been derived or what comparison was being made. No other statistical analyses were reported in either study. Tiacci et al 2021 reported a sample size calculation based on a hypothesised response rate but it was not stated what this was based on.

Both studies were considered to be at high risk of bias and certainty about the evidence for all critical and important outcomes was very low when assessed using modified GRADE. Factors reducing confidence in the outcomes include the lack of comparator groups, the small numbers of subjects and uncertainty about whether inclusion was complete and consecutive, the retrospective design and limited detail provided in Robak et al 2021, and the lack of statistical analysis.

No evidence was identified for the critical outcome of overall survival or the important outcomes of unplanned hospital admissions related to treatment-related adverse events, incidence of treatment-related infection, quality of life or activities of daily living. No evidence was identified on cost effectiveness.

7. Conclusion

This evidence review includes one prospective case series which recruited 31 patients and one retrospective case series including three patients which reported outcomes of treatment with vemurafenib plus rituximab in people with classic HCL who are refractory to, or later relapse following, treatment with second line PA therapy +/- rituximab, or patients with classic HCL who are unsuitable for PA therapy either first or second line.

The studies provide very low certainty evidence for the critical and important outcomes of progression free survival, relapse free survival, survival free of MRD, response to treatment and safety. No evidence was identified for the critical outcome of overall survival or the important outcomes of unplanned hospital admissions related to treatment-related adverse events, incidence of treatment-related infection, quality of life and activities of daily living, and no evidence on cost effectiveness was found.

The prospective case series reported that at median 37 months follow-up from the start of treatment progression free survival was 78%, and at median 34 months follow-up from the end of treatment relapse free survival among patients who had had a complete response to treatment was 85%. It also reported that patients who were MRD-negative after the end of treatment remained free of MRD at median 28.5 months follow-up.

The evidence from the prospective case series also found that 86.7% of patients had a complete response to treatment and 3.3% had a partial response (the remaining patients being unevaluable). In the retrospective case series with only three subjects, two had a complete response and one had a haematological response. Adverse events associated with treatment were common but most were low grade and all were reported to be transient. No patients were reported to have treatment-related infections.

Only one statistical analysis was reported in one study, the derivation of which was not clear. One study carried out some unplanned subgroup analyses which compared relapse free survival in patients who had had a complete response to treatment according to whether or not they had previously been treated with a BRAF inhibitor, whether or not they had MRD at the end of treatment, and whether or not they had previously had rituximab, but no statistical tests were reported so it is not possible to comment on the significance of these findings.

The very low certainty evidence identified suggests that the majority of patients with relapsed or refractory classic hairy cell leukaemia respond to treatment with vemurafenib plus rituximab, with few serious or sustained adverse effects. The limitations of the studies limit the strength of the conclusions that can be drawn and the lack of comparative data mean that no conclusions can be drawn about the effectiveness of vemurafenib plus rituximab compared with other treatments.

Appendix A PICO Document

The review questions for this evidence review are:

1. In people with classic HCL who are refractory to, or later relapse following, treatment with second line PA therapy +/- rituximab OR patients with classic HCL who are unsuitable for PA therapy either first or second line, what is the clinical effectiveness of vemurafenib plus rituximab plus standard care compared with standard care alone OR standard care with rituximab, interferon alpha-2a therapy, splenectomy or palliative care?
2. In people with classic HCL who are refractory to, or later relapse following, treatment with second line PA therapy +/- rituximab OR patients with classic HCL who are unsuitable for PA therapy either first or second line, what is the safety of vemurafenib plus rituximab plus standard care compared with standard care alone OR standard care with rituximab, interferon alpha-2a therapy, splenectomy or palliative care?
3. In people with classic HCL who are refractory to, or later relapse following, treatment with second line PA therapy +/- rituximab OR patients with classic HCL who are unsuitable for PA therapy either first or second line, what is the cost effectiveness of vemurafenib plus rituximab plus standard care compared with standard care alone OR standard care with rituximab, interferon alfa-2a therapy, splenectomy or palliative care?
4. From the evidence selected, are there any subgroups of patients that may benefit from vemurafenib plus rituximab more than the wider population of interest?
5. From the evidence selected, what was the treatment duration and dosing of vemurafenib plus rituximab in the population of interest?

P –Population and Indication	Patients with classic HCL who are refractory to, or later relapse following, treatment with second line purine nucleoside analogue (PA) therapy +/- rituximab OR Patients with classic HCL who are unsuitable for PA therapy either first or second line. [Classic HCL is characterised by a mutation called BRAF V600 which is present in all leukaemic cells. This differentiates classic HCL from hairy cell leukaemia variant (HCL-V), which does not harbour BRAF mutations.] [First line therapy is single agent PA therapy (with either cladribine or pentostatin) . The standard duration of treatment with cladribine monotherapy for classic HCL is 5 days (administered subcutaneously). Pentostatin is administered as a short intravenous infusion every 2-3 weeks, generally for 8-10 cycles, until remission is achieved. Second line PA therapy can be with either cladribine or pentostatin based on first line treatment and timing of relapse. For patients who are refractory to, or relapse within 2 years following PA therapy, standard second line treatment is generally with an alternative PA therapy (e.g., alternative to PA therapy administered as first line) in combination with rituximab. Patients who are refractory to, or relapse within 2-5 years following PA therapy, can be retreated with the initial PA therapy plus rituximab. Patients who relapse beyond 5 years from the end of initial treatment with PA therapy can be re-treated with the same, or an alternative, single agent PA therapy, plus

	or minus rituximab. Patients do not need to have received treatment with rituximab prior to receiving vemurafenib in combination with rituximab.] [Refractory disease is defined as a failure to achieve at least a partial response (PR) at the end of treatment with cladribine, or in the case of pentostatin, this would be at 6 months from treatment initiation. A PR is defined by the international consensus guidelines as requiring near normalisation of the peripheral blood count with a minimum of 50% improvement in organomegaly and bone marrow biopsy infiltration with HCL (Grever et al. 2017). Studies that do not apply this definition should also be included and any provided definition noted.] [Systemic purine nucleoside analogue therapy used in the treatment of classic HCL is with cladribine or pentostatin. Unsuitability for PA therapy will be determined in line with the SmPC for cladribine and pentostatin respectively. Contraindications for cladribine as indicated on the SmPC include: ○ Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. ○ Infection with human immunodeficiency virus (HIV). ○ Active chronic infection (tuberculosis or hepatitis). A delay in initiation of cladribine should also be considered in patients with acute infection until the infection is fully controlled. ○ Initiation of cladribine treatment in immunocompromised patients, including patients currently receiving immunosuppressive or myelosuppressive therapy (see section 4.5). ○ Active malignancy. ○ Moderate or severe renal impairment (creatinine clearance <60 mL/min) (see section 5.2). ○ Pregnancy and breast-feeding Contraindications for pentostatin as indicated on the SmPC include: ○ Pentostatin is contraindicated in patients who have demonstrated hypersensitivity to the active ingredient or to any of the excipients. ○ Pentostatin is contraindicated in patients with impaired renal function (Creatinine clearance < 60 ml/min). ○ Pentostatin is contraindicated in patients with active infection.]
I – Intervention	Vemurafenib + Rituximab + Standard Care [Vemurafenib is available as 240mg oral tablets. The recommended dose of vemurafenib for its licensed indication in the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma is 960mg twice daily. In some studies the dose of vemurafenib used for patients with relapsed or refractory classic HCL is either 240mg twice daily or 960mg twice daily.] [In most studies, rituximab is administered as an intravenous infusion at a dose of 375mg per square metre of body surface area every two weeks for a total duration of 16-18 weeks] [Standard care is considered to be symptom control, prophylactic antibiotics, transfusion support and pain relief as required]

C – Comparator(s)	Standard care alone OR Standard care in combination with any of the following: • Rituximab • Interferon alfa-2a therapy • Splenectomy • Palliative care
O – Outcomes	**<u>Clinical Effectiveness</u>** Minimally clinically important difference (MCIDs) are not known. <u>*Critical to decision-making:*</u> • **Overall Survival** *Overall survival is important to patients as individuals with relapsed or refractory HCL have a high mortality rate due to advanced disease. Improved overall survival is an important marker of effective treatment*. • **Progression free survival** *This outcome is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival and disease stability may result in patients experiencing fewer symptoms from the disease itself. It can be determined sooner than overall survival outcome measures*. • **Response to treatment** *Response to treatment is important to patients as it represents whether the treatment can improve disease burden.* [Disease response is measured by Minimal Residual Disease (MRD). MRD is defined as the lowest level of HCL cells that can be detected accurately and reproducibly using validated methods. MRD can be detected using bone marrow, peripheral blood or core biopsy. Other techniques for determining MRD include but may not be limited to: multiparametric flow cytometry (MRC) and PCR.] [For response to treatment, a timescale of 3-6 months would be of particular clinical relevance.] <u>*Important to decision-making:*</u> • **Unplanned hospital admissions due to treatment-related adverse events** *This is an important outcome to patients and their carers because it reflects the tolerability and adverse effects of the treatment. From a service delivery perspective, it reflects the demands placed on the healthcare system for the intervention.* [This outcome relates to unplanned hospital admissions that occur during the course of treatment.]

	• **Incidence of treatment-related infection** *This is an important outcome to patients and their carers because it is an important potential complication of treatment.* [This outcome relates to unplanned hospital admissions that occur during the course of treatment.] • **Quality of life** *Quality of life is important to patients as it provides an indication of an individual's general health, their self-perceived well-being and their ability to participate in activities of daily living. Measurement of quality of life can help inform patient-centred decision making and inform health policy.* [Examples of generic quality of life tools include QLQ-OV28, QLQ-C30 and the EQ-5D Examples of specific quality of life tools for patients with leukaemia include, but are not limited to: o Functional assessment of Cancer Therapy Leukaemia (FACT-Leu) o Life Ingredient Profile (LIP) o EORTC QLQ-CLL16 o MRC/EORTC QLQ-LEU] • **Activities of daily living (ADLs)** *ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home, and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation.* [ADLs can be measured using assessments such as: o Timed task completion (e.g., timed repeatable test such as dressing, meal preparation or patient specific ADL goal) o ADLs assessment using a tool (e.g., Barthel Index (BI) or Independence in Activities of Daily Living (ADL) o Subjective/self-reported assessment (e.g., by the individual, carer, or MDT. This could include self-reported questionnaires such as participation in work and other activities).] **<u>Safety</u>** *The safety of vemurafenib and rituximab is important to patients as it informs treatment decisions and allows comparison of interventional approaches.* [Examples of measures include, but are not limited to: • Frequency of adverse events • Frequency of grade 3 or 4 adverse events • Adverse events leading to discontinuation • Treatment related adverse events – e.g., skin rash, arthralgia, neutropenia, skin tumours, myelotoxicity, need for transfusion.] **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies.

	If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2013-2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library and the TRIP database were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2013 to 31 August 2023.

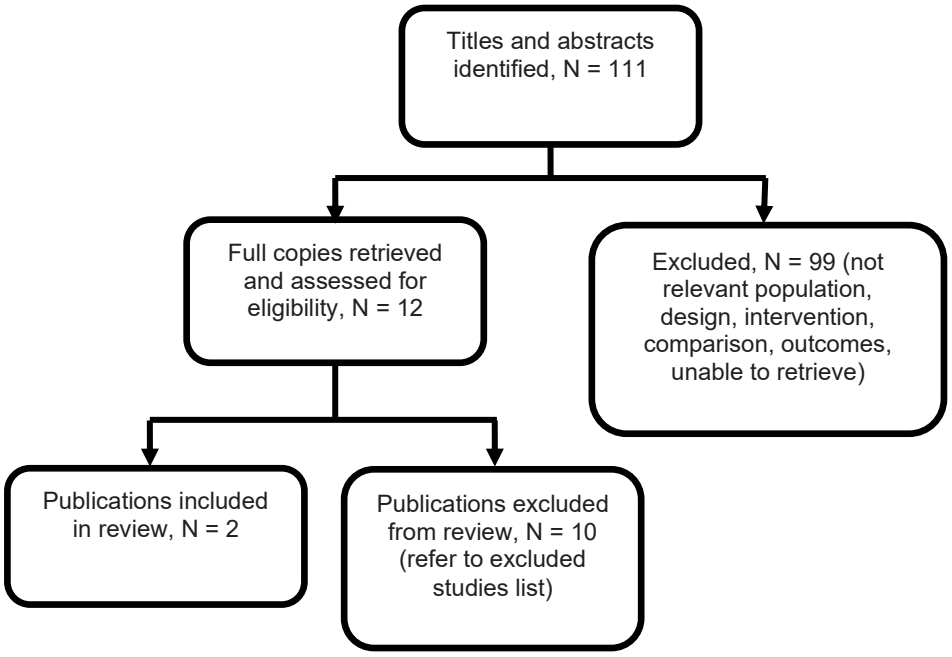
Medline search strategy:

1	Leukemia, Hairy Cell/
2	(hairy cell adj2 leuk?emia?).ti,ab,kf.
3	((leuk?emic or leuk?eia?) adj2 reticuloendothelios?s).ti,ab,kf.
4	1 or 2 or 3
5	Vemurafenib/
6	(vemurafenib or zelboraf).ti,ab,kf.
7	(vem* adj5 rit*).ti,ab,kf.
8	5 or 6 or 7
9	4 and 8
10	limit 9 to (english language and yr="2013 -Current")

Appendix C Evidence selection

The literature search identified 111 potential references. These were screened using their titles and abstracts and 12 references potentially relating to the use of Vemurafenib plus rituximab for relapsed or refractory classic hairy cell leukaemia were obtained and assessed for relevance. Of these, two references are included in this evidence review. The 10 references excluded are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Tiacci, E. *et al.* (2021) 'Vemurafenib plus rituximab in refractory or relapsed hairy-cell leukemia', *New England Journal of Medicine*, 384(19), pp. 1810–1823. doi:10.1056/nejmoa2031298.	Included in the review
Robak, T. *et al.* (2021) 'Vemurafenib and rituximab in patients with hairy cell leukemia previously treated with Moxetumomab Pasudotox, *Journal of Clinical Medicine*, 10(13), p. 2800. doi:10.3390/jcm10132800.	Included in the review
Dietrich, S. et al. (2016) 'BRAF inhibition in hairy cell leukemia with low-dose vemurafenib', Blood, 127(23), pp. 2847–2855. doi:10.1182/blood-2015-11-680074.	Excluded. No patients were treated with vemurafenib + rituximab

Appendix D Excluded studies table

Study reference	Reason for exclusion
Andrasiak I, Rybka J, Wrobel T. Response to the Therapy in Hairy Cell Leukemia: Systematic Review and Meta-Analysis. Clinical lymphoma, myeloma & leukemia. 2018;18(6):392-9.e3.	No studies used vemurafenib + rituximab
Bohn JP, Pircher A, Wanner D, Vill D, Foeger B, Wolf D, et al. Low-dose vemurafenib in hairy cell leukemia patients with active infection. American Journal of Hematology. 2019;94(6):E180-E2.	Letter
Dietrich S, Pircher A, Endris V, Peyrade F, Wendtner CM, Follows GA, et al. BRAF inhibition in hairy cell leukemia with low-dose vemurafenib. Blood. 2016;127(23):2847-55.	No patients were treated with vemurafenib + rituximab
Handa S, Lee JO, Derkach A, Stone RM, Saven A, Altman JK, et al. Long-term outcomes in patients with relapsed or refractory hairy cell leukemia treated with vemurafenib monotherapy. Blood. 2022;140(25):2663-71.	Patients received vemurafenib monotherapy
Konrat J, Rosler W, Roiss M, Meier-Abt F, Widmer CC, Balabanov S, et al. BRAF inhibitor treatment of classical hairy cell leukemia allows successful vaccination against SARS-CoV-2. Annals of Hematology. 2023;102(2):403-6.	Patients (n=3) were not refractory/relapsed and were initially given vemurafenib only.
Liebers N, Roider T, Bohn JP, Haberbosch I, Pircher A, Ferstl B, et al. BRAF inhibitor treatment in classic hairy cell leukemia: a long-term follow-up study of patients treated outside clinical trials. Leukemia. 2020;34(5):1454-7.	Letter
Moore JE, Delibert K, Baran AM, Evans AG, Liesveld JL, Zent CS. Targeted therapy for treatment of patients with classical hairy cell leukemia. Leukemia Research. 2021;102:106522.	Included 3 case reports of patients receiving vemurafenib + rituximab at some point but with different treatment regimes. Very limited reporting of patient characteristics and outcomes. Case reports therefore exclude.
Shenoi DP, Andritsos LA, Blachly JS, Rogers KA, Moran ME, Anghelina M, et al. Classic hairy cell leukemia complicated by pancytopenia and severe infection: a report of 3 cases treated with vemurafenib. Blood Advances. 2019;3(2):116-8.	Case reports, none received vemurafenib + rituximab as per PICO
Siddiqui R, Sardar M, Shahzad M, Jose J, Selene I, Shah Z, et al. Management of Relapsed Hairy Cell Leukemia: A Systematic Review of Novel Agents and Targeted Therapies. Clinical lymphoma, myeloma & leukemia. 2021;21(10):659-66.	Only one included study was said to include treatment with vemurafenib + rituximab, this reference was to a conference abstract so is not eligible to be included.
Tiacci E, Park JH, De Carolis L, Chung SS, Broccoli A, Scott S, et al. Targeting Mutant BRAF in Relapsed or Refractory Hairy-Cell Leukemia. New England Journal of Medicine. 2015;373(18):1733-47.	Patients received vemurafenib monotherapy

Appendix E Evidence Table

For abbreviations see list after table. For JBI checklist for case series see Appendix F.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Robak T, Janus A, Jamroziak K, Tiacci E, Kreitman RJ. Vemurafenib and Rituximab in Patients with Hairy Cell Leukemia Previously Treated with Moxetumomab Pasudotox. Journal of Clinical Medicine. 2021;10(13):25 **Study location** Lodz, Poland **Study type** Retrospective case record review **Study aim** To explore the optimal drug sequencing for relapsed/refractory HCL	Patients with classic HCL who had relapsed. **Inclusion criteria** Patients with classic HCL who had relapsed following treatment with Moxetumomab[18]. All were positive for BRAF p.V600E diagnosed by PCR. **Exclusion criteria** None stated **Total sample size** n=3 (A fourth patient included in the paper did not meet the PICO due to only receiving one dose of Rituximab) **Baseline**	**Intervention** Vemurafenib 240 mg twice daily for 16 weeks + rituximab 375mg/m^2 intravenously every 2 weeks x 8. (One of the 3 patients received Vemurafenib 960mg twice daily for the first 2 weeks before reducing to 240mg twice daily due to intolerance) **Comparison** No comparator group	The paper reports outcomes in patients who were still being followed up 3.5-4 years after completing their first treatment with vemurafenib + rituximab. **Critical outcomes** **Relapse free survival** (n=3) Relapse[19] free survival was reported in 3/3 at 13 months, 2/3 at 18 months and 1/3 at 38+ months after the end of treatment. **Response to treatment** Response to treatment was reported after the end of therapy. Complete response with no MRD: 2/3 patients[20] Haematological response[21]: 1/3 patient In one patient complete response was maintained at 38 months (at time of writing the paper).	This study was appraised using the JBI checklist for case series: 1. Yes 2. Unclear 3. No 4. Unclear 5. Unclear 6. Yes 7. Unclear 8. No 9. No 10. Not applicable **Other comments** This small retrospective case series described three patients with HCL treated with vemurafenib + rituximab following relapse after treatment with moxetumomab. All had had previous relapses after 2 or 3 courses of

[18] Note: the supply of moxetumomab has been discontinued in the USA by AstraZeneca because of 'insufficient use', and NICE has discontinued its appraisal of this drug stating that the company has advised that it is no longer pursuing a marketing authorisation application from the EMA.
[19] Relapse was not consistently defined in this study.
[20] Both patients were reported to have MRD-negative complete response; no further definition was provided
[21] Resolution of cytopaenia; no BM assessment was carried out

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study dates Vemurafenib + rituximab treatment was carried out between 2017-2019	**characteristics** Age range 28-53 years Male 2, Female 1 Time since first diagnosis 3.5 years to 14 years Patients had received 2 or 3 courses of cladribine previously (with or without rituximab); 2 had also previously received interferon α. Immediately before treatment with vemurafenib patients had relapsed after treatment with moxetumomab pasudotox which had achieved a complete or partial response.		**Safety** **Adverse events** [22] All patients were reported to have no serious adverse reactions to treatment with vemurafenib + rituximab. Details were not provided. No information was provided on whether any were associated with unplanned hospital admission.	treatment with cladribine (with or without rituximab). It was unclear whether identification of eligible patients was consecutive and complete. Details of HCL diagnosis were only provided for two patients but all had BRAF V600E mutation identified by PCR. Outcomes were not defined and details of outcome assessment were not provided. Very limited outcomes were reported and these were reported narratively with little detail. No details of adverse events were reported. **Source of funding:** The authors stated that the study was supported in part by grants from the Medical University of Lodz, Poland and from the Italian Ministry of Health.
Tiacci E, De Carolis L, Simonetti E, Capponi M, Ambrosetti A, Lucia E, et al. Vemurafenib plus	Patients with HCL who were refractory to, or had relapsed after, or were unsuitable for	**Intervention** Oral vemurafenib (960 mg twice daily[23]) for 8 weeks, and 8 intravenous	**Critical outcomes** **Progression free survival** (n=30)[24] Median follow-up 37 months (range, 0.5 to	This study was appraised using the JBI checklist for case series:

[22] Adverse events were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 but no details were reported
[23] One patient received vemurafenib at a dose of 720 mg twice daily owing to toxic effects during previous vemurafenib monotherapy
[24] Progression was defined as HCL-related death, relapse, or worsening of cytopaenias, whichever occurred first, after the start of treatment.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Rituximab in Refractory or Relapsed Hairy-Cell Leukemia. New England Journal of Medicine. 2021;384(19):1810-23. **Study location** Single centre in Perugia, Italy **Study type** Single group phase II study **Study aim** To assess the safety and efficacy of vemurafenib plus concurrent and sequential rituximab in patients with refractory or relapsed hairy cell leukemia (HCL) **Study dates** Recruitment March 2015 – June 2017	purine analogue (PA) therapy. **Inclusion criteria** Patients with HCL and mutated BRAF V600E who met any of the following criteria: primary refractoriness to a PA (defined as no response to first-line treatment or relapse within 1 year); early relapse (within 1 to 2 years) after the first course of a PA or at any time after a second or later course; severe side effects from PAs; ineligibility for chemotherapy; previous treatment with a BRAF inhibitor. In addition all patients had cytopaenia (Hb<11g/dl, neutrophil count <1500/mm^3, or platelet count	rituximab infusions (375 mg/m^2 of body-surface area) administered over a period of 18 weeks Treatment was administered in two cycles each consisting of 4 weeks of vemurafenib with rituximab infusions on days 1 and 15, followed by 2 weeks of rest and response evaluation. After the second cycle, four additional doses of rituximab were administered 2 weeks apart from one another. **Comparison** No comparator group	54.5) Progression-free survival from the start of treatment: 78% **Relapse free survival** (n=26 patients with complete response)[25] Median follow-up 34 months (range, 13 to 50) Relapse-free survival from the end of treatment: 85% (22/26) **Survival free from MRD (**n=17 patients who were MRD-negative after the end of treatment) Median follow-up 28.5 months (range, 21 to 50) after the MRD-negative status was first observed Survival free from MRD in both BM and peripheral blood: 100% **Response to treatment** (n=30[26]) The end-of-treatment response evaluation was conducted 4 weeks after the last dose of rituximab (i.e. 22 weeks from the start of treatment) 26/30 patients (86.7%) had *complete response*[27] at the end of treatment (p= 0.005)	1. Yes 2. Unclear 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. No 10. Unclear **Other comments** Patients were prospectively recruited to the study but it was not stated whether inclusion of eligible patients was consecutive or complete. Clear inclusion criteria were described. The details of HCL diagnosis were not described and the diagnosis of HCL was found to be incorrect in one patient shortly after inclusion. All patients had BRAF V600E mutation. Outcomes were clearly defined and length of follow-up was specified for all critical and important outcomes. Analyses

[25] Relapse was defined in this study as the reappearance of HCL-related cytopaenia in patients who had previously had a response at the end of treatment.
[26] One patient was withdrawn shortly after starting treatment as they were found to have an unclassifiable B-cell neoplasm instead of HCL.
[27] Complete response was defined as the resolution of cytopaenias (Hb≥11g/dl, neutrophil count ≥1500/mm^3, or platelet count ≥100,000/mm^3), no palpable splenomegaly, and no hairy cells morphologically visible in the BM biopsy and blood-smear samples

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	<100,000/mm^3). **Exclusion criteria** None stated Active infection was not an exclusion criterion. **Total sample size** n=31 **Baseline characteristics** Median age 61 years (range, 35 to 81); Male 28, Female 3 Median neutrophil count 686/ mm^3; Median platelet count 53,000//mm^3; 20/31 (65%) had splenomegaly. Patients had received a median of 3 (range 1-14) therapies previously. All had received a PA previously.		1/30 (3.3%) patient had a *partial response*[28] at the end of treatment 3/30 were reported to be not evaluable[29] Among the 26 patients with complete response: 17/26 (65%) had *no MRD*[30] **Important outcomes** **Incidence of treatment-related infection** (n =31) The authors reported that no patients experienced a treatment-related infection. **Safety** **Adverse events** (n=31, % affected)[31] Adverse events occurred in ≥20% of patients. Almost all were grade 1 or grade 2 and all were reported to be transient. No information was provided on whether any were associated with unplanned hospital admission. *Adverse events associated with rituximab:*	where appropriate were intention-to-treat. One p value was reported (for complete response) but it was not clear how it was derived and no other statistical analysis was reported. A sample size calculation was reported based on a hypothesised response rate but it was not stated what this was based on. A number of subgroup comparisons were reported, which were stated by the authors to be 'unplanned hypothesis-generating exploratory analyses'. **Source of funding:** The authors stated that study drugs were purchased with research funds that were provided by non-profit organizations and that were managed by the University of Perugia.

[28] Partial response was defined as the resolution of cytopaenias and a reduction of at least 50% in splenomegaly and in HCL infiltration in the BM biopsy sample on immunohistochemical testing
[29] One died after 10 days' treatment due to pre-existing infection; two did not receive full courses of treatment due to persistent toxic effects or concomitant myelodysplasia
[30] MRD was assessed in BM aspirates and in peripheral blood by means of allele-specific DNA PCR testing for BRAF V600E (sensitivity, ≥0.05% mutant copies).
[31] Toxic effects were graded according to the Common Terminology Criteria for Adverse Events, version 4.03.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	11/31 (35%) were refractory to that PA (including 8 with primary refractory disease). 2/31 (6%) were in late relapse and ineligible for further chemotherapy owing to side effects or contraindications to PAs. 15/31 (48%) had previously received interferon. 14/31 (45%) had previously received rituximab of whom 7/31 (23%) had disease that was refractory to rituximab either alone or in combination with a PA. 7/31 (23%) had a relapse after receipt of a BRAF inhibitor (vemurafenib or dabrafenib) after having had a complete, partial or minor response. 6/31 (19%) had disease that was refractory to the immediately preceding therapy.		Infusion-related reaction 9 (29%) *Adverse events associated with vemurafenib* Asymptomatic hyperbilirubinemia: 24 (77%) Asymptomatic increase in pancreatic enzymes: 18 (58%) Arthralgia or arthritis: 17 (55%) Rash or erythema: 15 (48%) Skin papilloma or warts 14 (45%) Asymptomatic increase in aspartate or alanine aminotransferase level: 9 (29%) Asymptomatic increase in γ-glutamyltransferase or alkaline phosphatase level: 9 (29%) Asymptomatic hypophosphatemia: 9 (29%) Anaemia: 7 (23%) Less frequent adverse events included transient neutropenia, photosensitivity, fever, nausea, hyperkeratosis, fatigue. No treatment-related infections were reported. *Toxic effects requiring reduction of dose of vemurafenib*: 14/29 These patients received 720mg or 480mg twice daily for at least 2 weeks. In 10/14 the dose was re-escalated once the toxic effects resolved. **Relapse free survival subgroup analyses** Relapse free survival in those with a complete response (total n=26; % in each group with the outcome):	

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			According to *previous treatment with BRAF inhibitor*: Median follow-up 34 months n=7 patients previously treated with a BRAF inhibitor: 57% n=19 patients not previously treated with a BRAF inhibitor: 95% According to *presence or absence of MRD:* Median follow-up not stated n=17 patients who had no MRD: 100% n=9 patients with MRD: 56% According to *previous exposure to rituximab:* Median follow-up not stated n=9 patients who had received rituximab previously: 89% n=17 patients who had not received rituximab previously: 82%	
Abbreviations BM: bone marrow; dl: decilitre; Hb: haemoglobin; HCL: hairy cell leukaemia; MRD: minimal residual disease; PA: purine analogue; PCR: polymerase chain reaction				

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for case series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No. of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Progression free survival (2 case series)									
Progression free survival from the start of treatment (%) at median 37 months follow-up (range 0.5 to 54.5)									
1 case series Tiacci et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	30	0	78%	Critical	Very low
Relapse[a] free survival (n) at between 13 and 38+ months after the end of treatment									
1 case series Robak et al 2021	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	3	0	3/3 at 13 months 2/3 at 18 months 1/3 at 38+ months	Critical	Very low
Relapse[b] free survival from the end of treatment (n, %) at median 34 months follow-up (range 13 to 50)									
1 case series Tiacci et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	26	0	22/26 (85%)	Critical	Very low
Survival free from minimal residual disease (MRD) after MRD-negative status first observed (%) at median 28.5 months follow-up (range 21 to 50)									
1 case series Tiacci et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	17	0	100%	Critical	Very low
Response to treatment (2 case series)									
Response to treatment[c] (n) after the end of therapy									
1 case series Robak et al 2021	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	3	0	Complete response: 2/3 Haematological response: 1/3	Critical	Very low
Response to treatment[d] (n, %) at 4 weeks after completion of treatment									
1 case series	Very serious	Serious indirectness[2]	Not applicable	Not calculable	30	0	Complete response: 26/30 (86.7%)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No. of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Tiacci et al 2021	limitations[4]						p= 0.005 Partial response: 1/30 (3.3%) Not evaluable: 3/30		
Absence of MRD among those who had a complete response to treatment (n, %) at 4 weeks after treatment completion									
1 case series Tiacci et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	26	0	No MRD: 17/26 (65%)	Critical	Very low
Incidence of treatment-related infection (1 case series)									
Incidence of treatment-related infection (n), duration of follow-up not stated									
1 case series Tiacci et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	31	0	Number of treatment-related infections reported: 0	Critical	Very low
Safety (2 case series)									
Serious adverse reactions associated with treatment with vemurafenib + rituximab (n)									
1 case series Robak et al 2021	Very serious limitations[1]	Very serious indirectness[3]	Not applicable	Not calculable	3	0	Serious adverse reactions: 0/3	Important	Very low
Adverse events (grade 1-4)[e] associated with treatment with rituximab or vemurafenib (n, %)									
1 case series Tiacci et al 2021	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	31	0	*Adverse events associated with rituximab:* Infusion-related reaction 9 (29%) *Adverse events associated with Vemurafenib* Asymptomatic hyperbilirubinemia: 24 (77%) Asymptomatic increase in pancreatic enzymes: 18 (58%) Arthralgia or arthritis: 17 (55%) Rash or erythema: 15 (48%) Skin papilloma or warts 14 (45%)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No. of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							Asymptomatic increase in aspartate or alanine aminotransferase level: 9 (29%) Asymptomatic increase in γ-glutamyltransferase or alkaline phosphatase level: 9 (29%) Asymptomatic hypophosphatemia: 9 (29%) Anaemia: 7 (23%) *Toxic effects requiring reduction of dose of vemurafenib*: 14/29 (48.3%) In 10/14 the dose was re-escalated once the toxic effects resolved		

Abbreviations
BM: bone marrow; MRD: minimal residual disease; n: number

1. Bias: very serious limitations due to unclear reporting of study participants in relation to consecutive and complete recruitment and lack of any statistical analysis
2. Indirectness: serious indirectness due to lack of comparator group
3. Indirectness: very serious indirectness due to lack of comparator group, lack of clinical information about study participants and lack of definition of outcomes
4. Bias: very serious limitations due to unclear reporting of study participants in relation to consecutive and complete recruitment and lack of information about the statistical result reported

a. Relapse was not consistently defined
b. Relapse was defined as the reappearance of HCL-related cytopaenia in patients who had previously had a response at the end of treatment.
c. Complete response was not consistently defined. Haematological response was defined as the resolution of cytopaenia.
d. Complete response was defined as the resolution of cytopaenias (Hb≥11g/dl, neutrophil count ≥1500/mm^3, or platelet count ≥100,000/mm^3), no palpable splenomegaly, and no hairy cells morphologically visible in the BM biopsy and blood-smear samples. Partial response was defined as the resolution of cytopaenias and a reduction of at least 50% in splenomegaly and in HCL infiltration in the BM biopsy sample on immunohistochemical testing.
e. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03.

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

References

Included studies

Robak T, Janus A, Jamroziak K, Tiacci E, Kreitman RJ. Vemurafenib and Rituximab in Patients with Hairy Cell Leukemia Previously Treated with Moxetumomab Pasudotox. Journal of Clinical Medicine. 2021;10(13):25

Tiacci E, De Carolis L, Simonetti E, Capponi M, Ambrosetti A, Lucia E, et al. Vemurafenib plus Rituximab in Refractory or Relapsed Hairy-Cell Leukemia. New England Journal of Medicine. 2021;384(19):1810-23.

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